Quality in Chemical Measurements: A Three-Legged Stool

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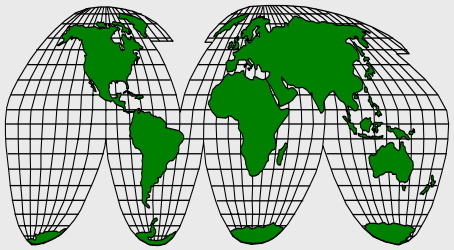
Increasing Interest and Requirements for *Traceable* Chemical Measurements

- **National and International Trade**
- **Environmental Decision-Making**
- **Assessing Food Quality**
- **Healthcare Decision-Making**

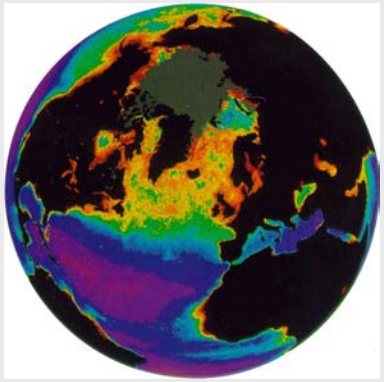


Mercury in the Environment

- On February 24, 1998 EPA issued a report to Congress on air toxics emissions from the utility industry. *"…on balance, mercury from coal-fired utilities is the hazardous air pollutant of greatest public health concern."*

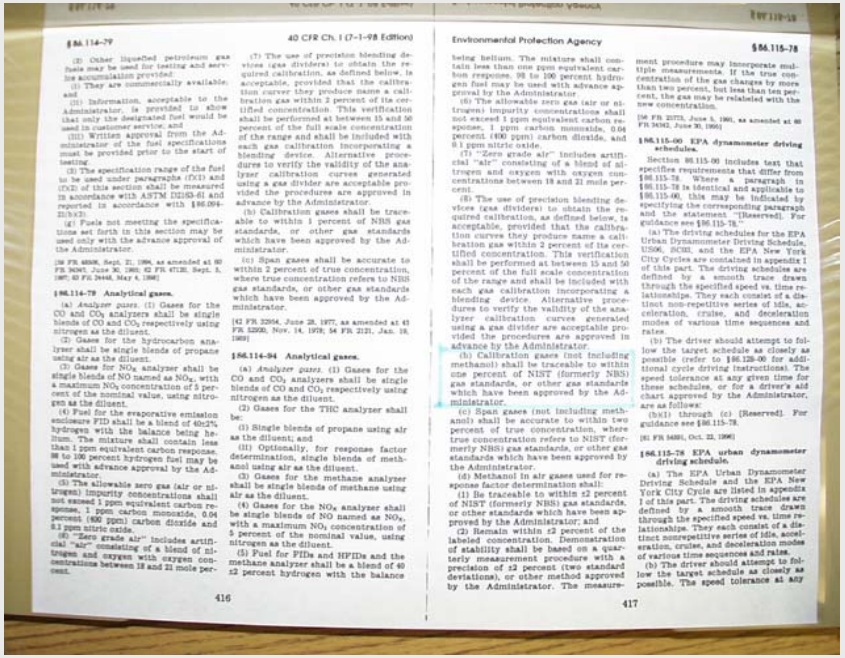
- EPA is to regulate Hg air emissions from coal-fired power plants, which contribute a third (50 tons) of the anthropogenic Hg released to the environment each year
- Hg bio-accumulates as the highly toxic species methylmercury in the aquatic environment, the primary source of risk to human health being consumption of fish (freshwater and marine). The NRC estimated that *"… ~60,000 US children may be born each year with neurological defects resulting from in utero exposure to Hg in seafood."*

- FDA report states: *"Commercial fish sold through interstate commerce that are found to have levels of methylmercury above an "action level" of 1 ppm cannot be sold to the public."*



Traceability to stated references
… and global confidence in this realization . . .
are the basis for
mutual recognition and confidence in data
used to facilitate and underpin international trade
and decisions regarding health, safety, commerce,
and/or scientific studies

40 CFR Part 86.114(b)



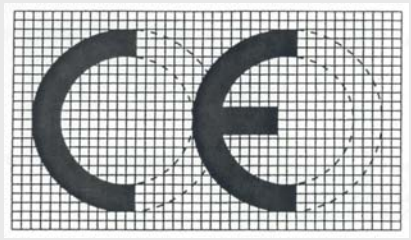
"…Calibration Gases (not including methanol) shall be traceable to within one percent of NIST (formerly NBS) gas standards, or other gases as approved by the Administrator…"

New Regulatory Requirement: EU IVD Directive

A New Driver:
EU IVD Directive to go into effect 2003

Stated Purpose of Directive

- **Eliminate trade barriers *within Europe* by ensuring access to the entire EU market with one single product approval (CE Mark)**



Essential Requirements

- **IVD Calibrators and/or control materials must be *"traceable to standards of a higher order"***
  - **nationally/internationally recognized *certified reference materials***

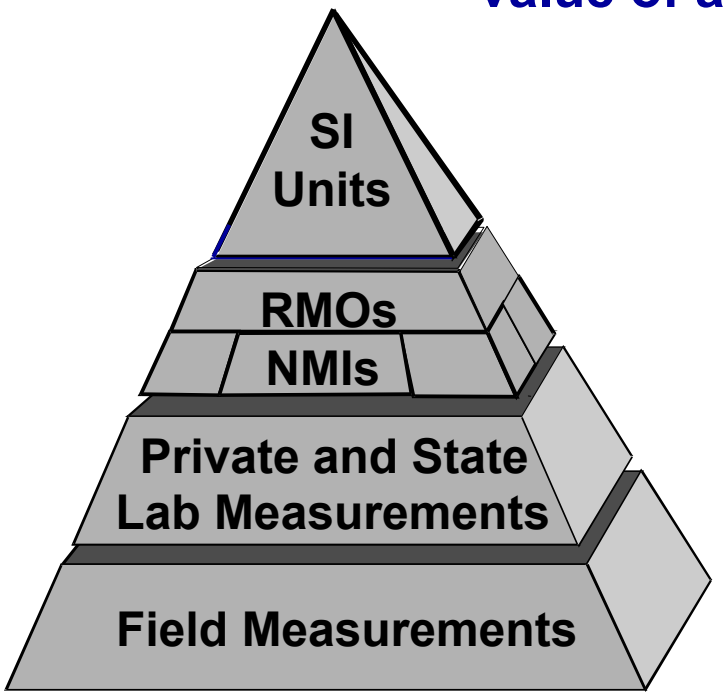
Scheduled Implementation

- **First IVD product with CE Mark may be placed from June 2000 onwards**
- **All *new* IVD products *must* have mark by December 2003 (may be delayed)**
- **Existing IVD products may be sold without the CE mark until December 2005**

European Union *In Vitro* Diagnostics Devices Directive

- "...the traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or reference materials of higher order..."

Traceability: The property of the result of a measurement or the value of a standard whereby it can be related to **stated references**, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties. (VIM)



Uncertainty (of measurement): "A parameter associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand."

Traceability and global comparability are the basis for mutual recognition … and international trade ... and confidence in data used in making decisions relating to health, safety, commerce, and/or scientific excellence.

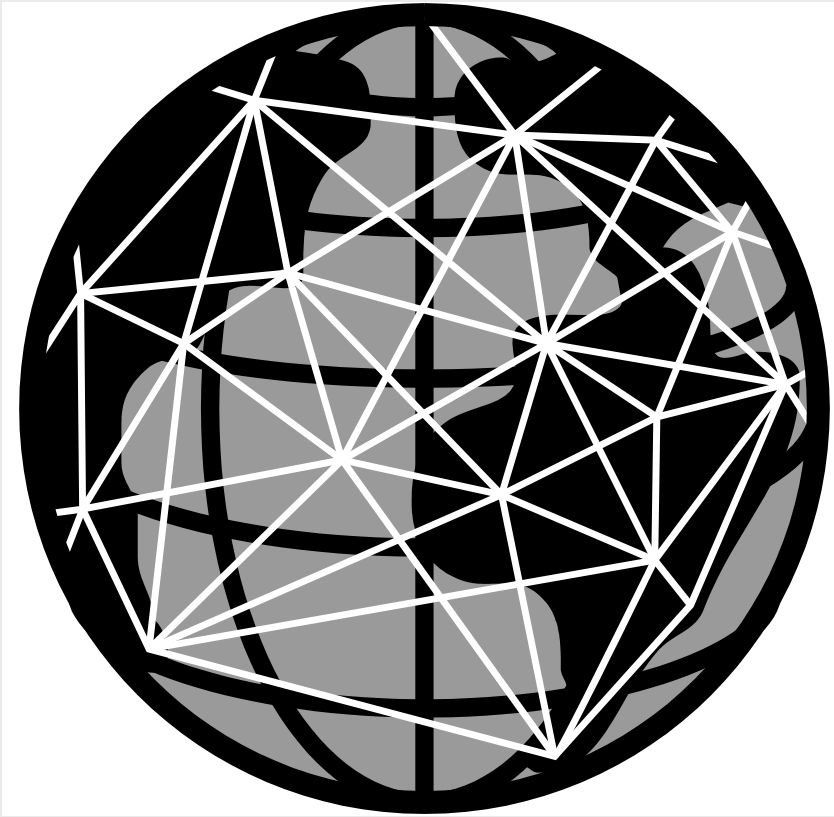
(**VIM**: **I**nternational **V**ocabulary of basic and general standard terms in **M**etrology, ISO, Geneva, Switzerland, 1993, 6.10)

Comparing results

- results are only useful when compared
  - to other results
    - e.g., to observe a trend
  - to limits
    - e.g., a threshold for action
  - different results in different places or measured at different times…
    - *"comparability over space-and-time"*

Comparability of results

- Whole and sole goal of traceability.
  - *raison d'être!*
- results linked to a common reference can be compared
- scope of reference defines scope of comparability
  - global network
    - SI



For Chemical Measurements:

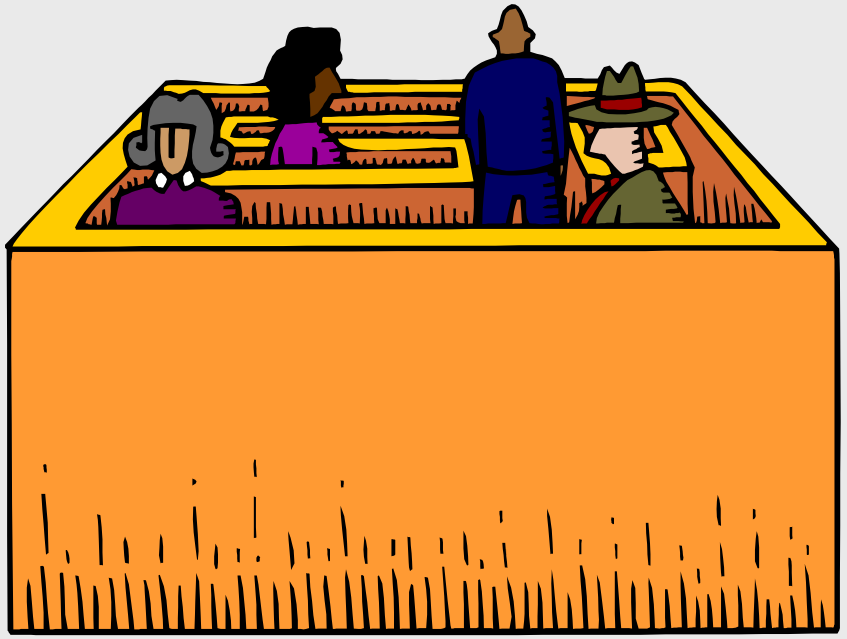
"Traceability" does not assure "Quality"

- traceability isn't an umbrella under which we can hide
  - it's *part* of quality
- being traceable, even to a good reference, doesn't mean you're right!
- *all it does is let us compare results*

"Traceability in chemistry is different!"

- "…formidable difficulties exist in establishing international traceability for measurements in chemistry."

  20th Conférence Générale des Poids et Mesures, 1995



Traceability in chemistry…

- is different.
  - identity
    - what am I measuring, anyway?
  - interference
    - do I get the same response for analyte in my calibration material and in it's matrix?
  - morphology
    - is the analysis the same everywhere in my sample?

Biochemical Markers for Heart Attack

- EKGs often do not show evidence of heart damage
- Damage to heart tissue is accompanied by a rise in blood levels of certain proteins

- CK-MB	not specific to heart tissue
- Troponin I	specific to heart tissue

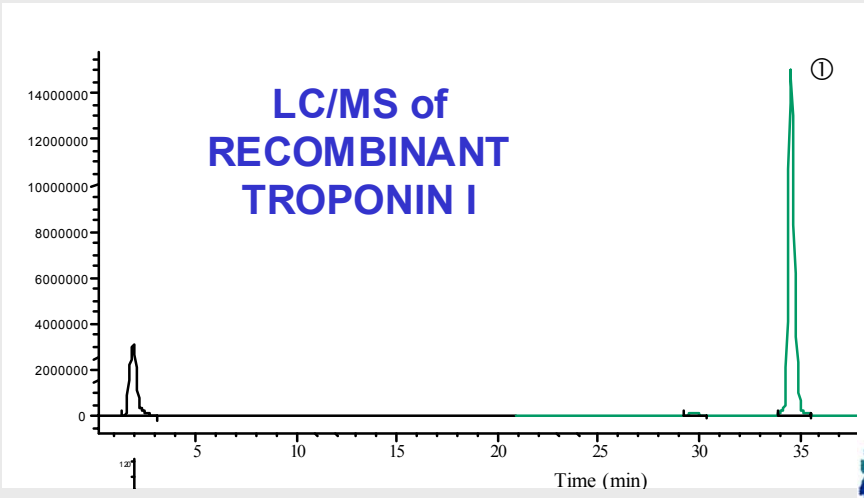
- Immunoassay-based methods are used to measure blood troponin levels
- Results among various immunoassays vary by more than 20-fold on same blood sample

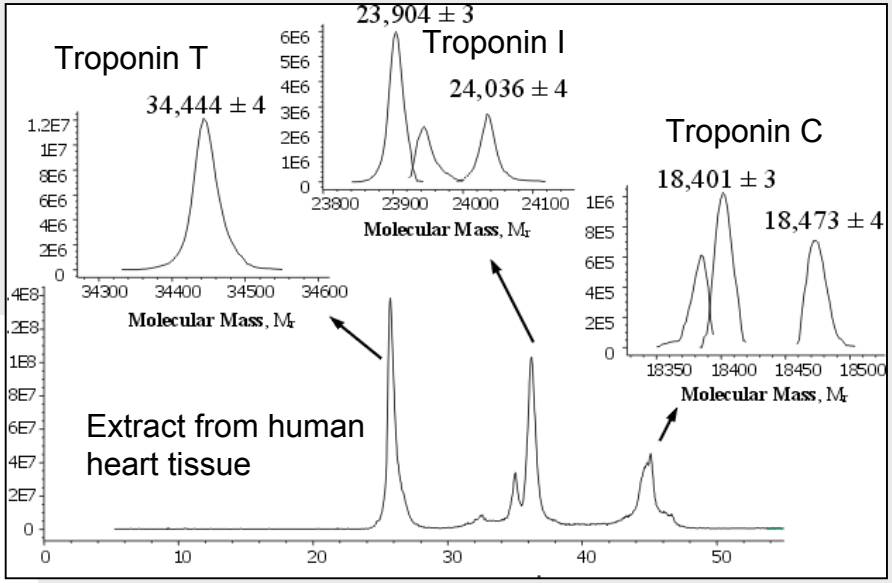
Assay Manufacturer	Conc. ng/mL	# Labs
A	19.9	115
B	6.7	489
C	0.85	27

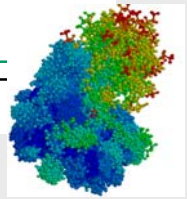
From G. S. Bodor, Denver Health and Hospitals -- personal communication 1997

Troponin I

The measurement of cTnI in serum provides a highly selective and sensitive means for diagnosing myocardial infarction, *BUT METHOD COMPARABILITY IS VERY POOR.*







PROBLEM:

Troponin I is a complex, heterogeneous protein that may be free or may be complexed with Troponin C and/or Troponin T. Different assay antibodies do not recognize the same form.

WHAT IS NIST DOING?

- **Working with the AACC and IFCC to identify which Troponin I form best harmonizes immunoassay results**
- **Developing a purified troponin I SRM for calibrating immunoassays**
- **Developing reference method and SRM for troponin I in blood**

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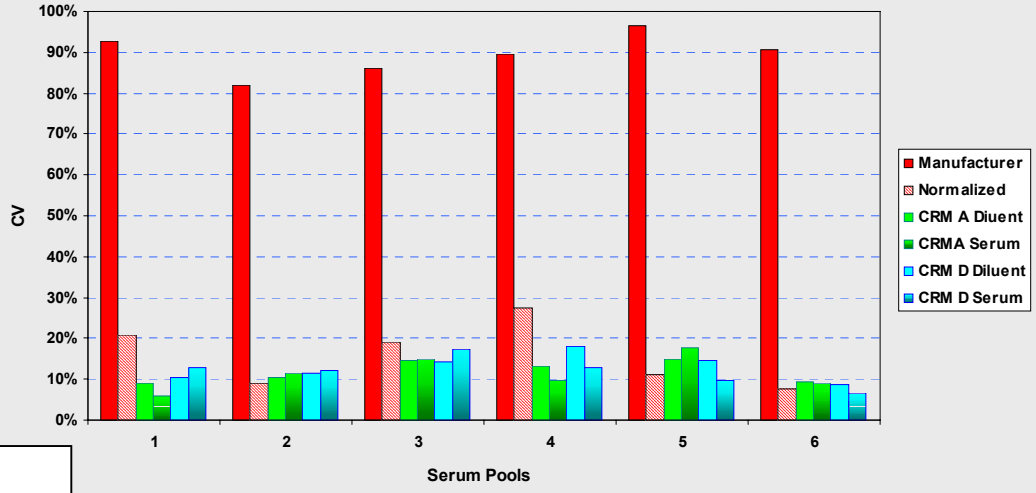

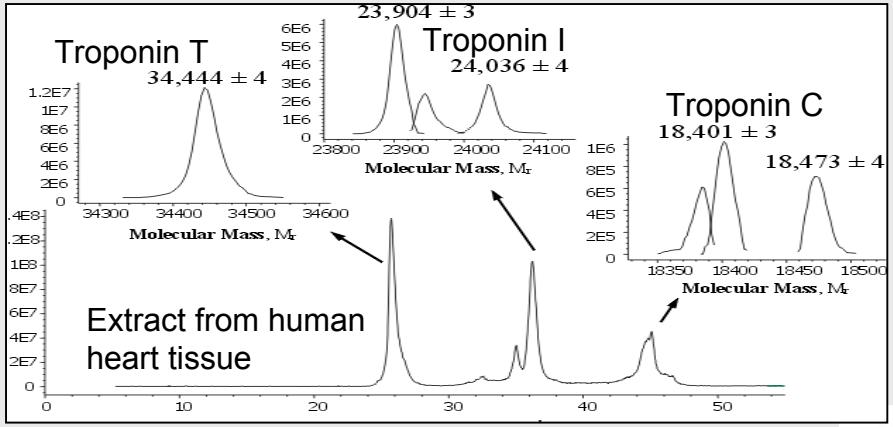

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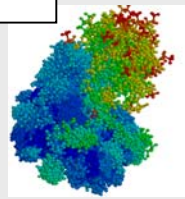
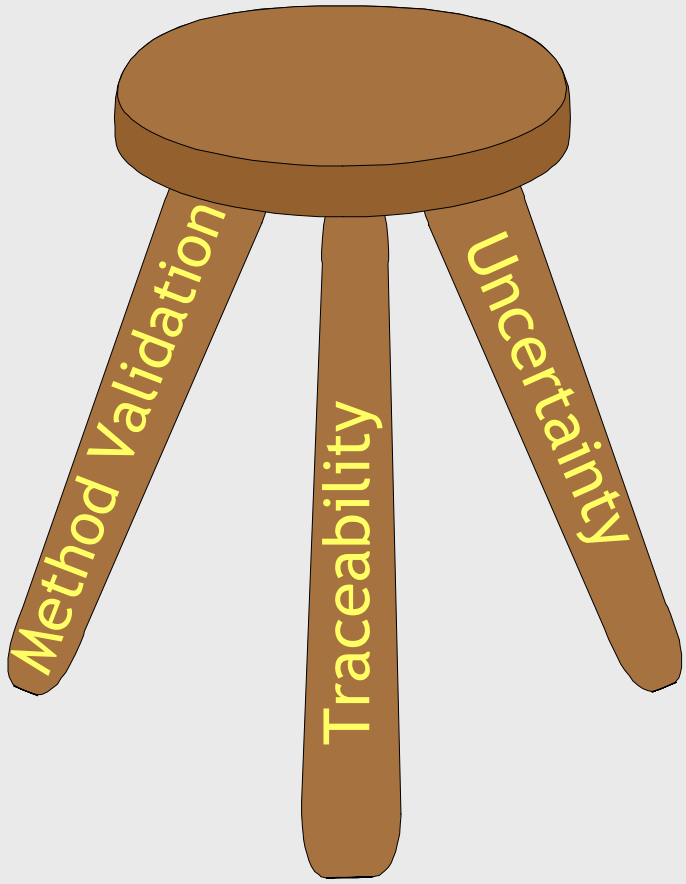


Project Highlights

- **Completed two round-robins with the AACC that identified the best material for use as a calibrant to harmonize results**
- **Material identified is a CIT complex from human heart. Concentration will be certified at NIST.**
- **Future plans are to develop a reference method and SRM for troponin I in blood**

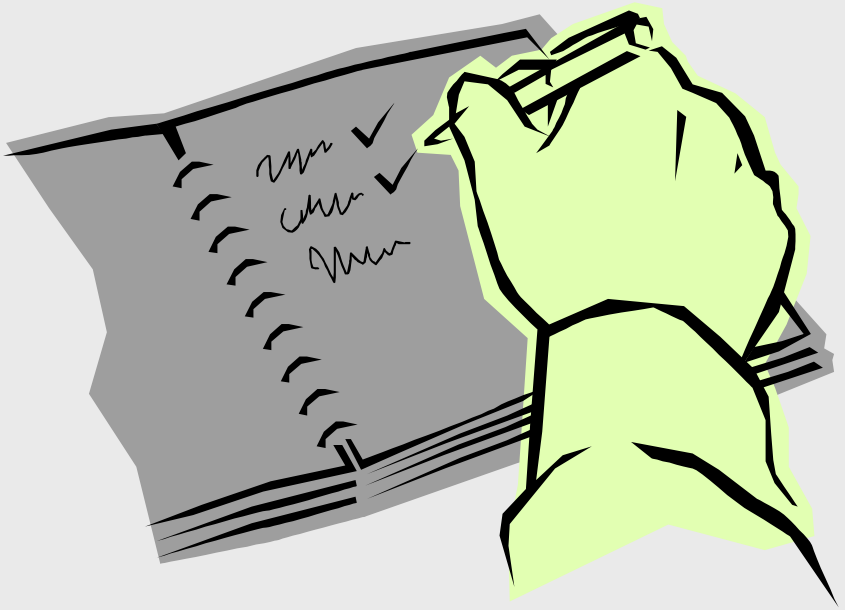
“Quality” in Chemical Measurements

- traceability of result
  - can I compare this result with other results
- method validation
  - am I measuring what I set out to measure?
- uncertainty
  - how well do I know the result of what I’ve measured?



Method validation

- checks the model
  - tests completeness
  - tests assumptions
  - helps establish an uncertainty budget
  - assure that the analyte is what's being measured
  - robustness w.r.t. interference
- identifies relevant parameters to keep under control
- tests scope



Reference Materials and the Three-Legged Stool

- traceability
  - calibration to common references
  - permits comparison of results
- method validation
  - test the model
  - *"Prime Meridian"*
- uncertainty
  - evaluate bias
  - control charting
    - *need stability, not accuracy*

Traceability in chemistry…

- is different.
  - the fallacy is that valid methods have…
    - defined scope
    - clear measurement model
      - assure that the analyte is what's being measured
      - robustness w.r.t. interference

Measurement model

$$C_{Unknown} = \frac{C_{Standard}}{S_{Standard}} S_{Unknown}$$

- if you get this part right…
  - you've demonstrated that…
    - you know what you're measuring
    - it's not affected by other stuff
  - you know how to keep your method in control

Chromium (mg/kg) in CRM HISS-1 Marine Sediment (NRC Canada)

NRC GFAAS	NRC ID - ICPMS	NIST INAA
10.9 ± 1.1	11.7 ± 1.3	31.4 ± 4.5

National Research Council Canada | Conseil national de recherches Canada

Footnote on HISS-1 Certificate

"†Chromium in HISS-1

It became apparent during the certification of HISS-1 that there is a significant fraction of Cr that is not easily solubilized. The certified value of 30 mg/kg was obtained using solid sampling techniques or prolonged digestion with hydrofluoric, sulphuric and perchloric acids. Less vigorous acid dissolution techniques (including microwave heating using closed vessels at high pressure) result in Cr values between 10 and 13 mg/kg."

NRC · CNRC

CRMs for method validation

- establish ‘quality’ of measurement
  - deploy method with known performance
  - use series/”suite” of CRMs to establish scope
    - *‘How far does the light shine?’*
- *Matrix CRMs play vital role in method validation and uncertainty estimation*

NIST Standards for Chemical Measurements

- High Purity Neat Chemicals
- Organic Calibration Solutions
- Inorganic Calibration Solutions
- Gas Mixture Standards

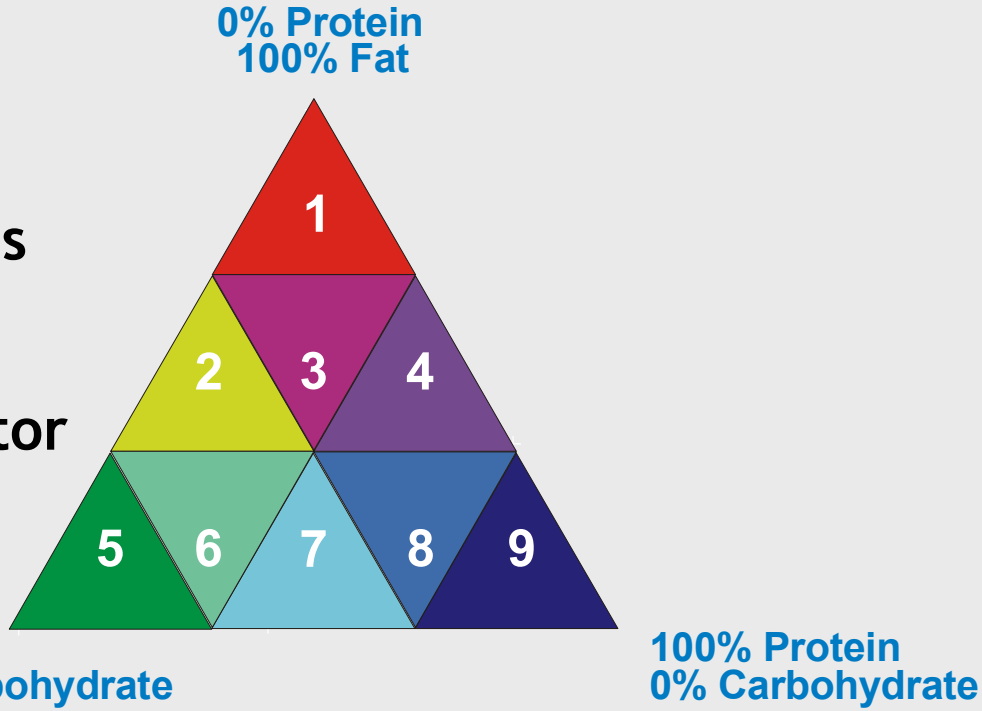
Complex Matrix Standards

- Advanced Materials
- Biological Fluids/Tissues
- Foods/Botanicals
- Geologicals
- Metal Alloys
- Petroleum/Fossil Fuels
- Sediments/Soils/Particulates

- Optical Filter Standards
- Electrolytic Conductivity Standards
- Ion Activity Standards

AOAC Food Triangle

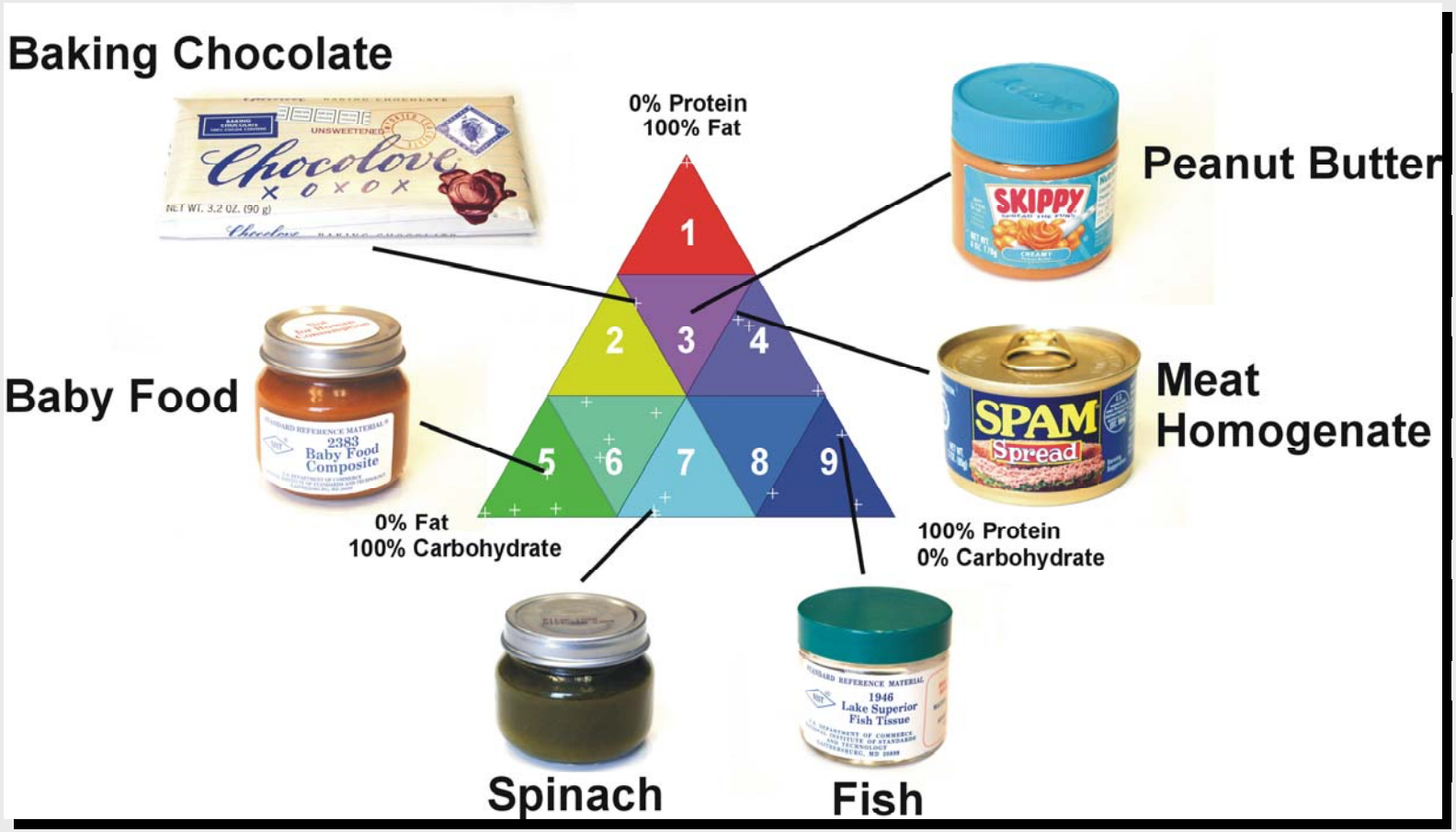
- Established to address NLEA
- Analytical methods and reference materials must be valid for each sector



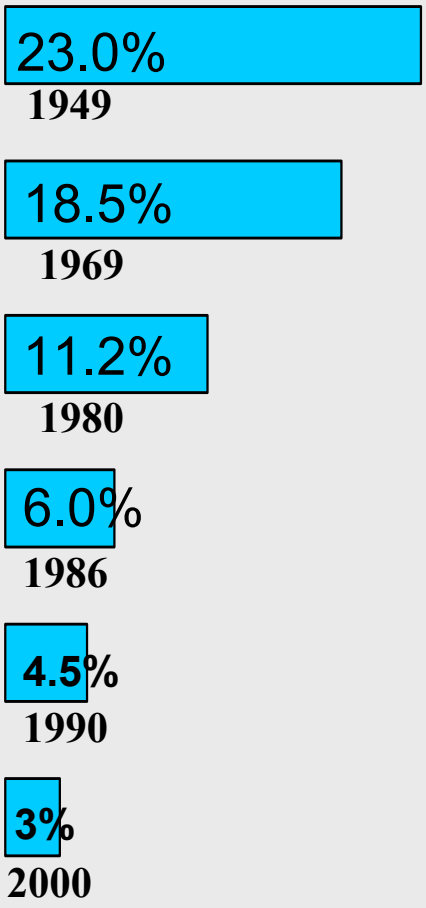
"The food matrix organizational scheme can be used to select one or two food matrices representing each sector, for development of a series of reference materials representing all foods. In some sectors, several samples may be necessary to account for differences in all the types of protein, fat, or carbohydrate."

W. R. Wolf and K. W. Andrews, "A System for Defining Reference Materials Applicable to All Food Matrices", **Fresenius' J. Anal. Chem.** 1995 353:73-76

Food-matrix Standard Reference Materials



Precision of Cholesterol Measurements in Clinical Laboratories and NIST Contributions



NIST Activities

1967 - Pure Cholesterol SRM

1980 - Cholesterol in Serum Definitive Method

1981 - First Cholesterol in Human Serum SRM

1988 - New Suite of Cholesterol in Serum SRMs at Medical Decision Points

1997 - New Suite of Cholesterol in Serum SRMs designed to address clinical analyzer commutability issues; HDL-, LDL-Cholesterol and Triglyceride values provided

Improvement in precision since 1969 has been estimated to save $100M/yr in treatment costs

Development of SRMs for Herbal Dietary Supplements

NIST Partners

- National Institutes of Health, Office of Dietary Supplements (NIH-ODS)

  Senate Language FY2002

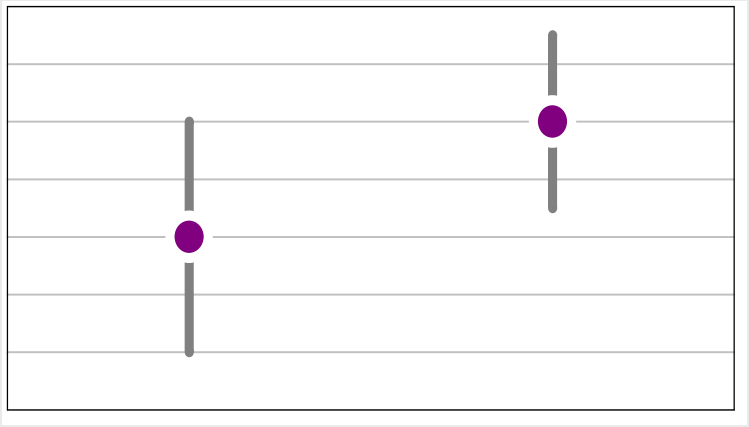
  "NIH-ODS to allocate sufficient funds to speed up an ongoing collaborative effort to develop and *disseminate validated analytical methods* and *reference materials* for the most commonly used botanicals and other dietary supplements."

- Food and Drug Administration, Center for Food Safety and Applied Nutrition (CFSAN) & Center for Drug Evaluation and Research (CDER)

- AOAC Dietary Supplement Task Group
  - FDA
  - Trade associations (five)
  - National Research Council of Canada
  - U.S. Pharmacopeia
  - NIST
  - Industry representatives
  - Contract laboratories

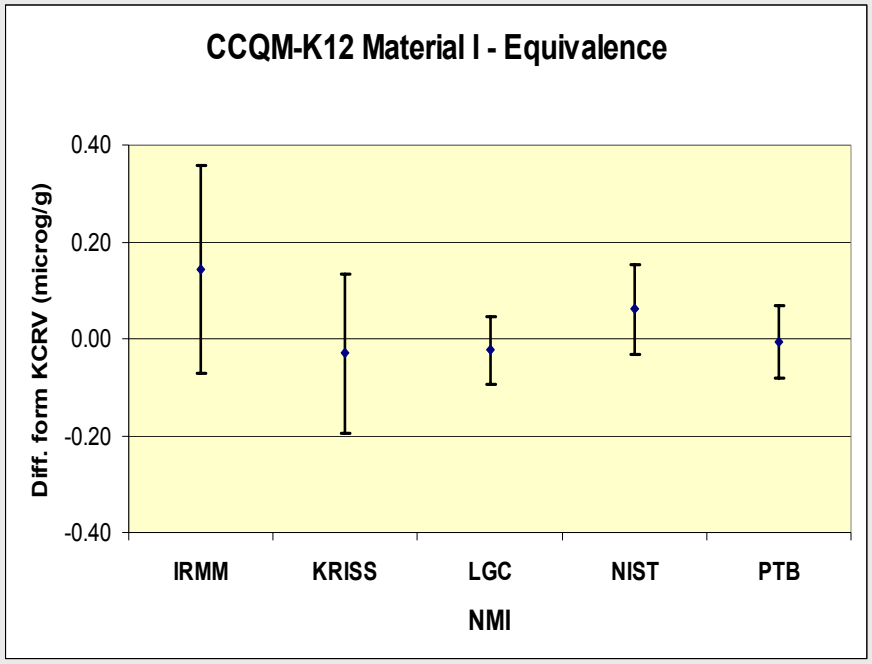
Uncertainty budget

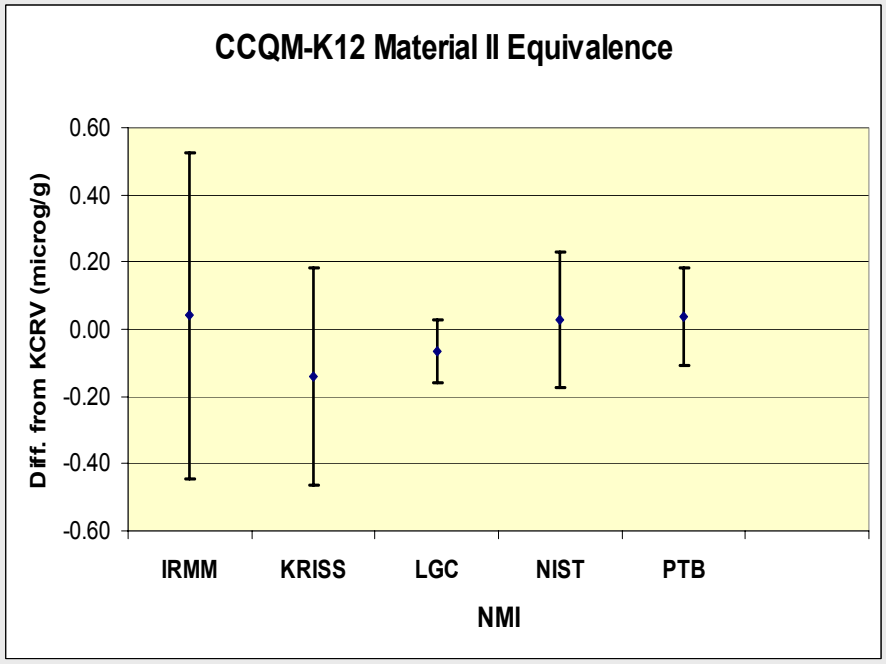
- how well do you know the result?
  - essential part of being able to compare!
    - are these two results the same???
- are these results good enough?
  - fit-for-purpose



CCQM- K12 Creatinine in Serum

NIST served as pilot laboratory for this study and the two study samples were IMEP-17 materials I and II.



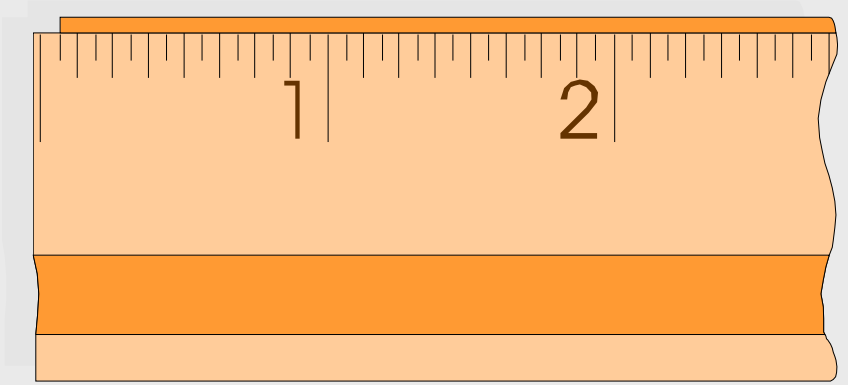


KCRV = Key Comparison Reference Value

Good agreement was achieved for both materials among laboratories using either GC/MS- or LC/MS-based methods

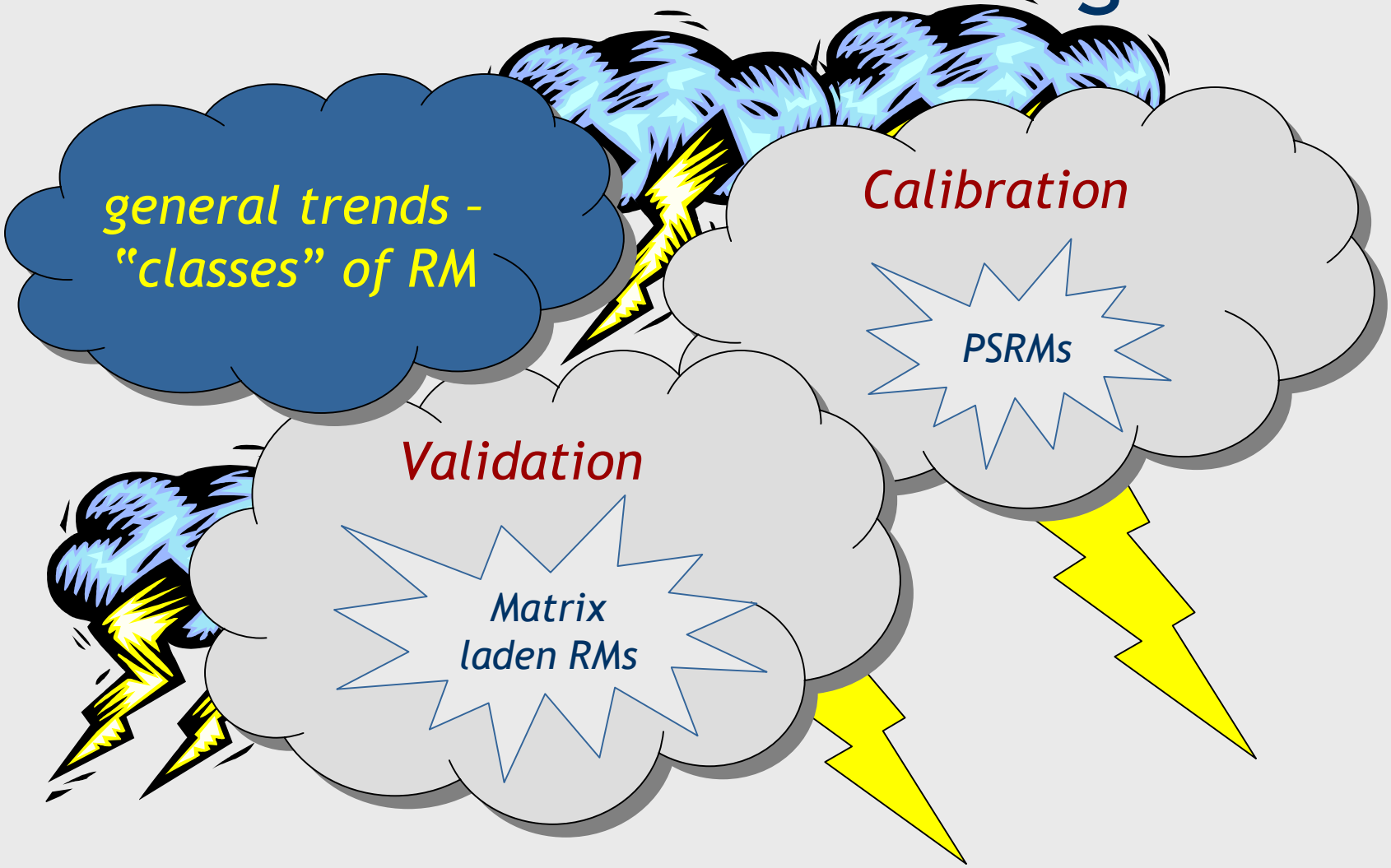
Traceability

- *Traceability* is how you get units on your result
  - in our simple model, convert from units of your measurement tool to units of the 'standard'
- *'standards' may appear in several places in model!*
  - where 'correction' is required
    - *'recovery'*



$$C_{Unknown} = \frac{C_{Standard}}{S_{Standard}} S_{Unknown} \cdot \left(\frac{Added}{Found} \right)$$

Reference material usage…



CRMs for method validation

- "I ran a CRM, and…
  - I got the right answer."
    - useful i… there…
  - I got the answer."
    - also useful information here!

remember what method validation is doing…

RMs for validation

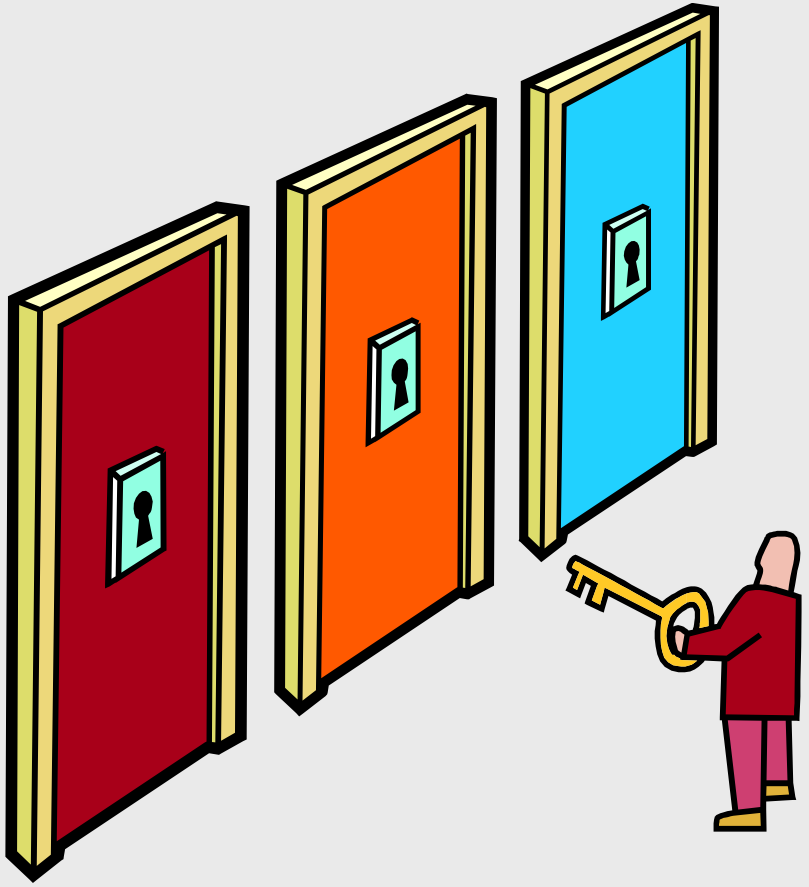
- good selection requires understanding of…
  - chemistry of the sample
  - chemistry of the validation material
  - physics of the measurement

Calibration materials

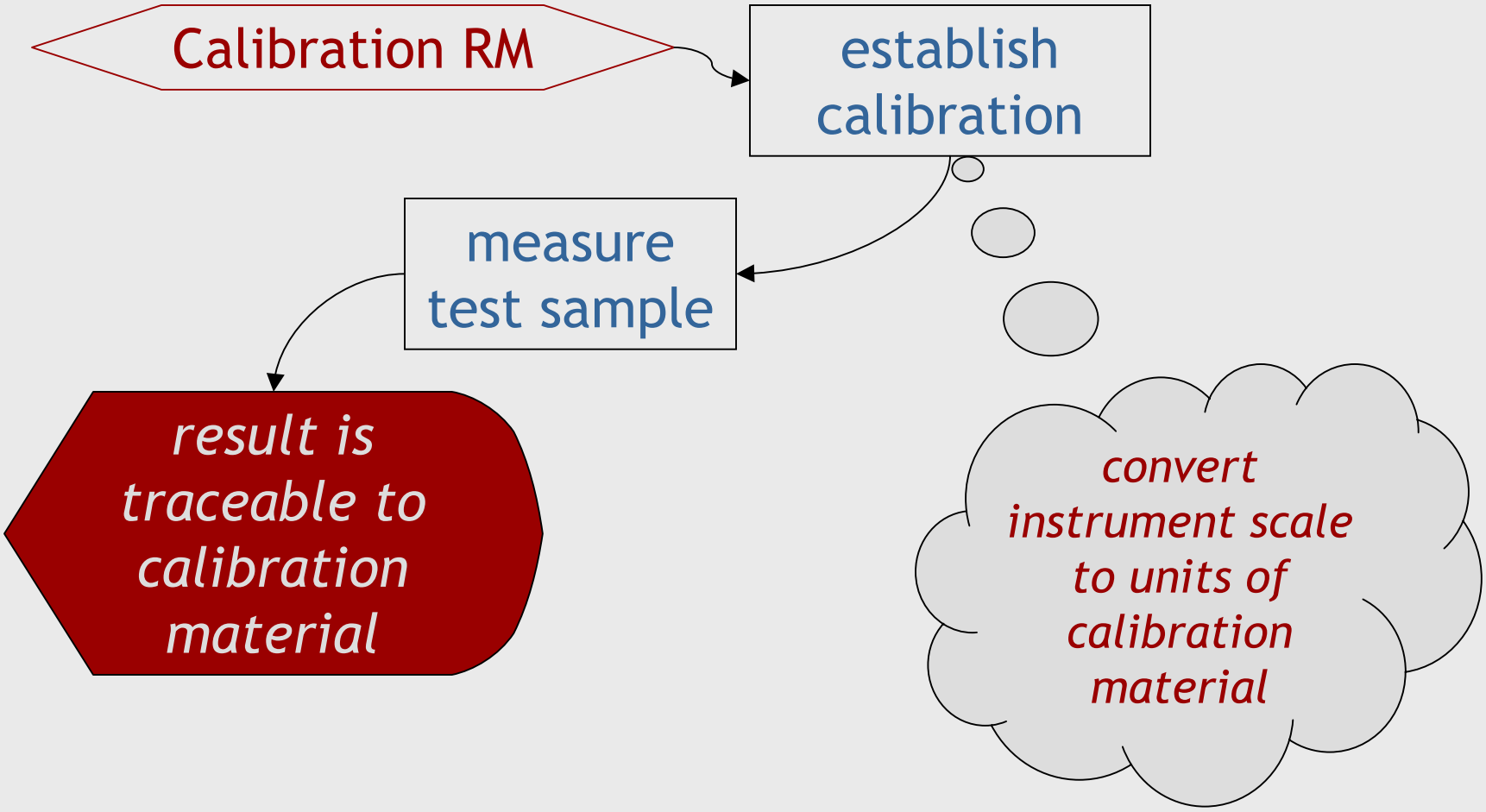
- *traceability of reference determines scope of traceability of results!*
  - local traceability gives local comparability
  - global traceability gives global comparability
- PSRMs traceable to SI
  - *global scope!*
  - purity determination
    - source of value
    - source of uncert.

Calibration materials

- PSRMs
  - no matrix
    - applicable to many…
  - reagent grade materials often suitable
    - fit-for-purpose
- require knowledge…
  - physics
  - chemistry of PSRM
  - chemistry of sample
- regulatory compliance
  - may require **CRM**
  - may require scope



Establishing Traceability…



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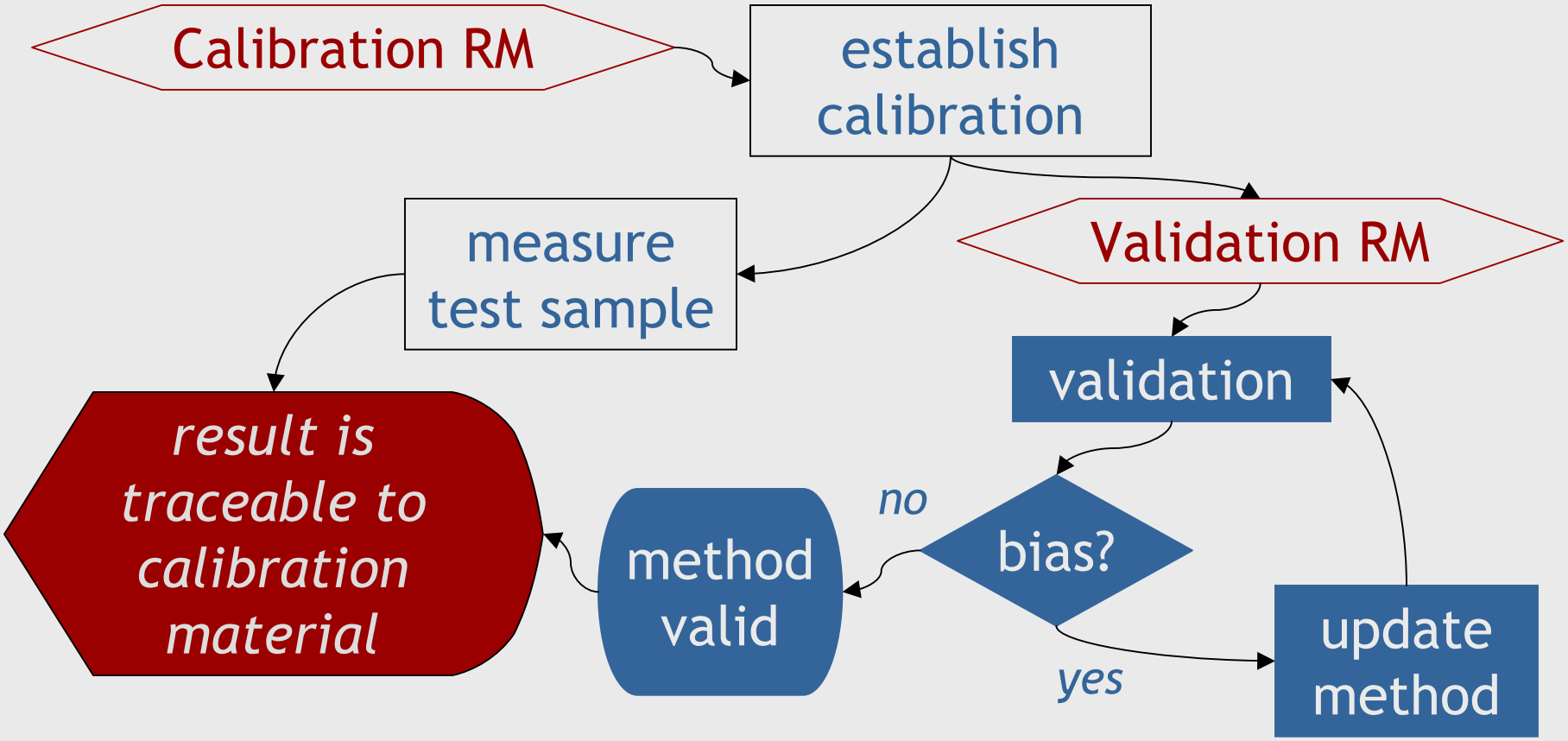

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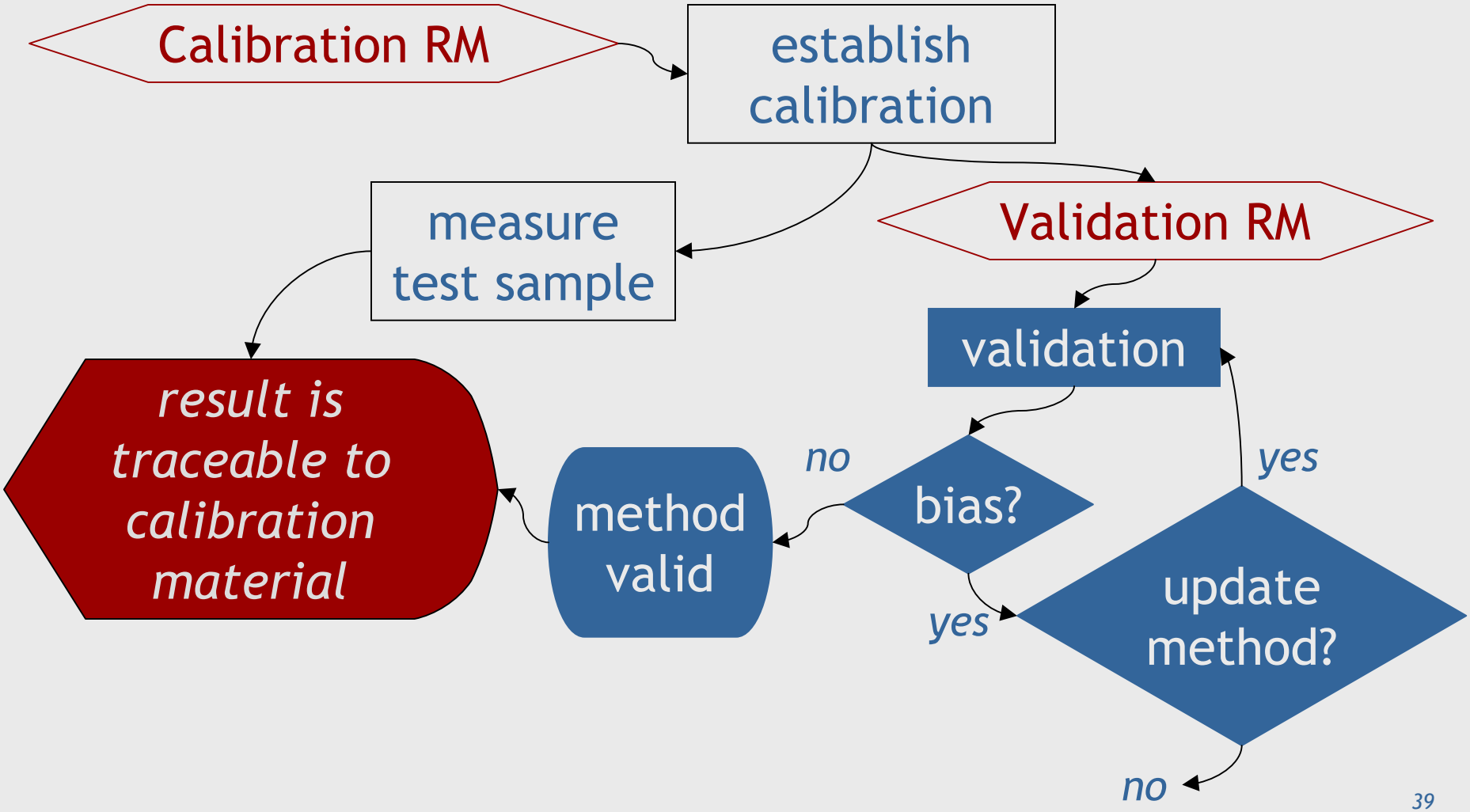

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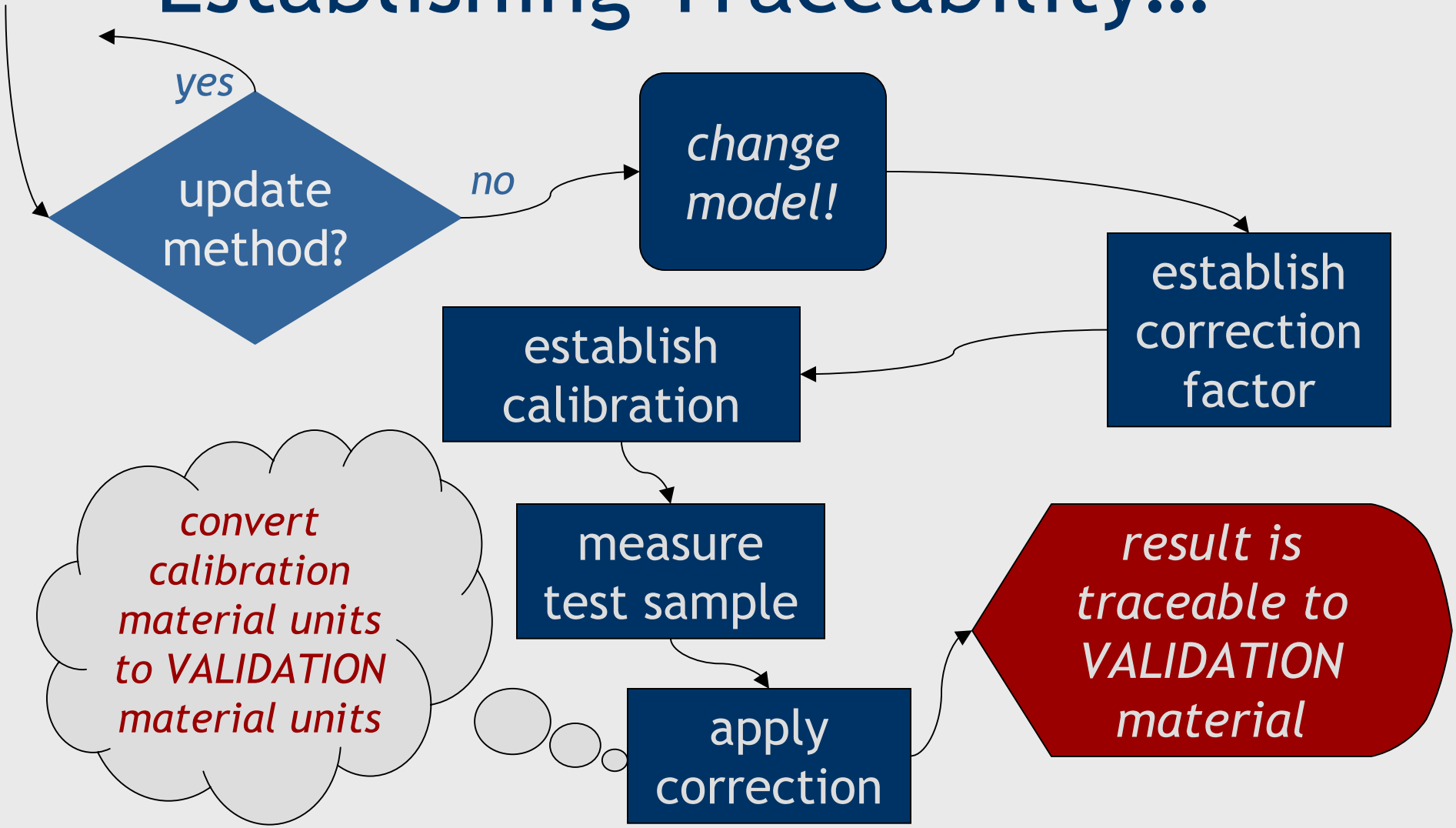
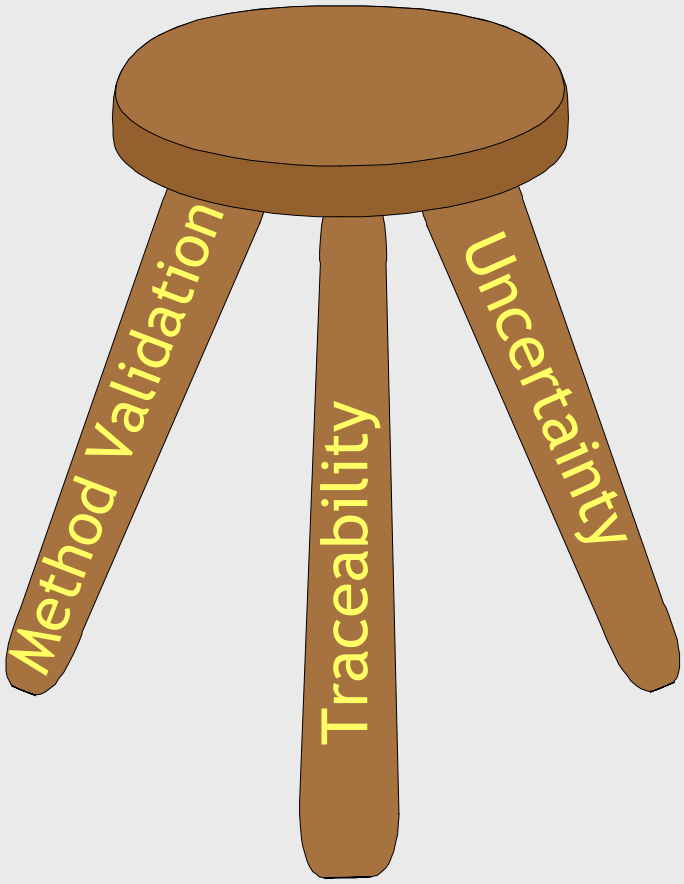


Achieving "Quality" in Chemical Measurements

- traceability of result
- Validated Method
- Robust Uncertainty Budget



Matrix CRMs *v.* PSRMs

- Matrix CRMs
  - leverage the best measurements!
    - expensive, high-effort techniques to certify
    - information xfer to less expensive tools
  - matrix-match?
  - uncertainty
    - fit-for-purpose?
    - homogeneity?
  - *INTENDED FOR METHOD VALIDATION*
- PSRMs
  - small uncertainty
    - often stable
    - homogeneous
    - no morphology
  - realization of the kilogram or the mole
    - traceability to SI
  - purity determination often very certain
  - more easily reproduced
  - more easily deployed
  - *needs valid method!*
  - *INTENDED FOR CALIBRATION*